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JAMA Insights

Dengue

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Epidemiology

Dengue is a mosquito-borne illness caused by dengue viruses 1 through 4. Dengue has resurged globally with larger outbreaks in endemic areas and new cases in nonendemic regions, facilitated by range expansion of vector mosquito populations and climate change, population growth, and urbanization.[1]

Dengue is a growing health threat in the US. In 2023, the US Centers for Disease Control and Prevention (CDC) reported 1890 travel-associated cases.[2,3] As more travelers return to the US with dengue virus infection, the risk of local mosquito-borne transmission increases. *Aedes aegypti* and *Aedes albopictus* mosquitoes, which can become infected and spread dengue virus if they bite an infected person (eg, returning travelers), are present in many states. Although dengue virus transmission in US states is uncommon, locally acquired cases are reported regularly from south Florida, with 189 cases identified in 2023. Between 2010 and 2023, locally acquired cases have also been reported in Hawai'i (250), Texas (40), Arizona (2), and California (2).

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Transmission

Dengue virus transmission is primarily vector-borne through *Ae aegypti* and *Ae albopictus* mosquitoes present in tropical and subtropical regions worldwide. Although less common, infection can also be bloodborne through perinatal transmission, mucocutaneous exposure to infected blood, blood donation, organ transplantation, or possibly sexual transmission.[1]

Clinical Presentation

Approximately 75% of people with dengue virus infection are asymptomatic. Patients with symptomatic dengue virus infection typically present with high fever (≥38.5 °C) and nonspecific symptoms, including myalgias, arthralgias, nausea, vomiting, headache, and macular or maculopapular rash, up to 2 weeks after being bitten by infected mosquitoes. Illness occurs in 3 phases: febrile, critical, and recovery. The febrile phase usually lasts 2 to 7 days. The critical phase, when patients are at highest risk for severe disease, begins at defervescence and lasts 24 to 48 hours. Most patients (>95%) improve during this time; however, warning signs, including severe abdominal pain or tenderness, persistent vomiting, extravascular fluid accumulation (pleural effusion, ascites, or pericardial effusion), mucosal bleeding (gums, nose, vagina, or kidney), altered mental status, hepatomegaly, or progressive increase in hematocrit, indicate increased risk for progression to severe dengue (previously classified as dengue hemorrhagic fever or dengue shock syndrome).[4] In a surveillance study from Puerto Rico including 1432 dengue cases from 2012 to 2022, the most frequently reported warning signs were abdominal pain (869 [61%]) and altered mental status (699 [49%]).[5] Plasma leakage was the most common manifestation of severe disease, reported in 18% of cases, representing 66% of all severe dengue cases.

Approximately 5% of cases can progress rapidly to severe dengue, which may involve hypovolemic shock, gastrointestinal or vaginal bleeding requiring transfusion, and end-organ impairment (eg, liver, heart, central nervous system). During the recovery phase, patients with plasma leakage experience reabsorption of extravasated fluids, potentially leading to volume overload, particularly if volume replacement exceeds dengue management guidelines. In the Puerto Rico analysis of 1432 patients with dengue infections, 263 (18%) had dengue without warning signs, 788 (55%) had warning signs without severe dengue, 381 (27%) had severe dengue, and 2 patients (0.1%) died. In addition to fever, the most frequently reported findings were headache (1200 [84%]), myalgias (1066 [74%]), and leukopenia (1022 [71%]).[5]

Diagnosis

Dengue should be suspected in febrile patients living in or returning from dengue-endemic areas (particularly areas experiencing dengue outbreaks) and considered in patients with signs and symptoms compatible with dengue in areas with *Aedes* mosquito vectors. The differential diagnosis includes infections such as chikungunya, Zika, leptospirosis, malaria, influenza, and COVID-19 and noninfectious etiologies such as leukemia or Kawasaki disease.[5]

Patients with suspected dengue should be tested using a combination of reverse transcriptase–polymerase chain reaction (RT-PCR) (or nonstructural protein 1 [NS1] antigen enzyme-linked immunosorbent assay [ELISA]) and IgM antibody tests. Dengue virus is usually detectable by RT-PCR or NS1 ELISA during the first week of illness, while IgM antibodies rise during the first week and remain detectable for at least 3 months. A single positive IgG antibody result is not diagnostic of acute infection, as it may indicate a past infection with dengue or another flavivirus, such as Zika. Paired IgG results in acute and convalescent specimens can provide evidence of infection through seroconversion or a 4-fold or greater change in titers. Point-of-care tests are available, but none are US Food and Drug Administration approved for use in the US.

Risk Factors for Severe Dengue

Populations at higher risk for progression to severe dengue include pregnant people, infants (aged <1 year), older adults (aged >65 years), and patients with comorbidities such as diabetes, obesity, hypertension, asthma, coagulopathy, gastritis or peptic ulcer disease, chronic liver disease, or kidney disease. A meta-analysis of 122 observational studies reported the risk of severe dengue was 31% (135/431) among patients with diabetes vs 16% (868/5421) without diabetes (odds ratio [OR], 4.38 [95% CI, 2.58-7.43]); 35% (240/685) among patients with hypertension vs 21% (763/3695) without hypertension (OR, 2.19 [95% CI, 1.36-3.53]); 46% (44/96) among patients with kidney disease vs 16% (271/1690) without kidney disease (OR, 4.67 [95% CI, 2.21-9.88]); and 23% (9/39) among patients with cardiovascular disease vs 9% (155/1793) without cardiovascular disease (OR, 2.79 [95% CI, 1.04-7.50]).[6] Infection with 1 dengue

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virus only confers immunity to that specific virus; individuals experiencing a second infection with a different dengue virus have a higher risk for severe dengue compared with a first infection (11.8% [1682/14 252] with prior infection vs 5.2% [507/9660] without prior infection; OR, 2.26 [95% CI, 1.65-3.09]) because of antibody-dependent enhancement, which occurs when antibodies bind but do not neutralize dengue virus and instead facilitate entry and replication in immune cells.[7]

Clinical Management

Patients with a presumptive diagnosis of dengue should be managed according to CDC guidelines while test results are pending. Treatment is supportive. Patients without warning signs or comorbidities may be managed in the outpatient setting with advice to stay hydrated with oral fluids and monitor for warning signs, particularly around the time of defervescence. Patients with warning signs, coexisting conditions (pregnancy, coagulopathy, infancy [<1 year], older age [>65 years], diabetes, obesity, hypertension, asthma, gastritis or peptic ulcer disease, chronic liver disease, or kidney disease), or severe dengue require hospitalization and intravenous fluids following CDC guidelines. Close monitoring for warning signs and prompt initiation of intravenous fluids can prevent hypovolemic shock and reduce mortality to less than 1%.[8] However, patients should be closely monitored for fluid overload and intravenous fluids should be discontinued when plasma leakage resolves.

Prevention

People can decrease their risk of acquiring dengue by using US Environmental Protection Agency–registered insect repellents with DEET, picaridin, IR3535, oil of lemon eucalyptus, para-Menthane-3,8-diol, or 2-undecanone; wearing clothing that covers arms and legs; and staying in lodging with screened windows and doors and air conditioning. Eliminating mosquito breeding sites (cleaning or removing water-holding containers) can also help reduce the spread of disease.

Use of insecticides to control *Aedes* species mosquitoes is limited by high levels of insecticide resistance worldwide. Novel vector control methods include introduction of mosquitoes infected with *Wolbachia*, bacteria that decrease the ability of mosquitos to transmit several viruses, and have shown protective efficacy of up to 77% in reducing symptomatic dengue.[9]

Dengue vaccines aim to protect against all 4 dengue viruses. Dengvaxia is the only vaccine recommended for use in the US; however, production has been discontinued due to lack of global demand. Qdenga, a 2-dose vaccine, protects against all 4 dengue viruses among people with a previous dengue infection (seropositives) and against dengue viruses 1 and 2 among people with no previous dengue infection (seronegatives). The vaccine provided no efficacy against dengue viruses 3 or 4 among seronegatives, and data were insufficient to rule out increased risk of symptomatic illness or hospitalization during a subsequent dengue infection. Because the highest rates of infection and hospitalizations in dengue-endemic areas are among children, the World Health Organization recommends Qdenga for children and adolescents aged 6 to 16 years in endemic areas with high dengue transmission intensity characterized by high IgG seropositivity rates (seroprevalence) in younger age groups.

Conclusions

Dengue incidence is increasing worldwide. Clinicians should consider the diagnosis of dengue in febrile travelers returning from endemic areas and among patients with compatible signs and symptoms in areas of the US with *Aedes* mosquito vectors. Appropriate case identification and clinical management can improve patient outcomes and reduce mortality to less than 1%.[10]

ARTICLE INFORMATION

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Note: Source references are available through embedded hyperlinks in the article text online.

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